Seizure (2007) **16**, 527–532

SEIZURE

www.elsevier.com/locate/yseiz

Randomized study of intravenous valproate and phenytoin in status epilepticus

Puneet Agarwal *, Navneet Kumar, Rakesh Chandra, Gaurav Gupta, Arun Raj Antony, Niren Garg

Neurology Unit, KPS PG Institute of Medicine, GSVM Medical College, Kanpur 208002, India

Received 7 January 2007; received in revised form 7 April 2007; accepted 16 April 2007

KEYWORDS
Status epilepticus;
Benzodiazepine refractory status epilepticus;
Intravenous phenytoin;
Intravenous valproate

Summary

Introduction: The evidence based data to guide management in patients of benzodiazepine refractory status epilepticus (SE) is still lacking. We conducted a randomized study to evaluate the comparative effect of intravenous (IV) phenytoin and intravenous valproate (IV VA) in patients of benzodiazepine refractory SE.
Background and methods: Hundred, age and sex matched, patients of benzodiazepine refractory SE were randomly divided into Group A (50 patients), treated with IV VA and Group B (50 patients) treated with IV phenytoin. Twelve patients, in whom SE was not controlled with a single drug, were switched over to the other group. Treatment was considered successful when all motor or EEG seizure activity ceased within 20 min after the beginning of the drug infusion and no return of seizure activity during the next 12 h. Secondary study end points were adverse events to treatment, in-hospital complications and the neurological outcome at discharge.
Results: In this study, IV VA was successful in 88% and IV phenytoin in 84% ($p > 0.05$) of patients of SE with a significantly better response in patients of SE <2 h ($p < 0.05$). The total number of adverse events did not differ significantly between the two groups ($p > 0.05$). There were no differences among the treatments with respect to recurrence after 12-h study period or the outcome at 7 days.
Conclusion: IV VA is as effective as IV phenytoin. It is easy to use, better tolerated and can be used as an alternative to IV phenytoin in patients of benzodiazepine refractory SE, especially in patients of cardio-respiratory disease. The better outcome in patients having shorter duration of SE (<2 h) suggests need of immediate treatment.

Introduction

Approximately 5% of adult and 10–25% of children with epilepsy have at least one episode of status

* Corresponding author. Tel.: +91 512 2535617; fax: +91 512 2535617.
E-mail addresses: pgpuneet@gmail.com, agpuneet@hotmail.com (P. Agarwal).

1059-1311/$ – see front matter
doi:10.1016/j.seizure.2007.04.012

epilepticus (SE) during the course of their disease.[1–3] SE is present in nearly all epileptic syndromes, even idiopathic ones, although it is more frequent in cryptogenic and symptomatic forms.[4] Phenobarbital,[5–7] phenytoin,[8–10] diazepam plus phenytoin[11,12]and lorazepam[13–15] have been advocated for the initial treatment of SE, and each is used by a substantial number of physicians. No randomized controlled data supporting phenytoin as a second line treatment are available, but one uncontrolled study suggested that 50% of patients not successfully treated with a benzodiazepine alone would respond to a second line treatment (usually phenytoin).[16] Traditionally, based on a long clinical experience, and case controlled studies, intravenous (IV) phenytoin has been used as the second drug.

Starting in the 1980s, the use of intravenous valproate (IV VA) has been reported in an increasing number of uncontrolled case series, indicating relative ease of use, relatively good tolerability and suggesting that it may be efficacious.[17] In one study, 20 adult patients in acute or static SE with generalized tonic–clonic seizures (GTCS) or simple partial motor seizures were administered IV valproic acid in a bolus dose of 15 mg/kg body weight and then as a continuous infusion of 1 mg/kg/h for 24 h safely. SE was interrupted in less than 30 min in 80% of cases.[18] Recently, there are other reports about successful use of IV VA in controlling SE[19,20] but there is no randomized comparative study to the best of our knowledge till now. Hence, we planned a randomized study to demonstrate the efficacy and safety of IV VA as the initial therapy for controlling seizures in patients of SE refractory to diazepam, and to compare it with IV phenytoin.

Materials and methods

This study was conducted on patients of status epilepticus refractory to IV diazepam admitted in emergency ward and intensive care unit from December 2004 to February 2006. The definition of SE is based on the clinical manifestations—a prolonged seizure or a series of seizures during which the patient has incomplete recovery of consciousness, and duration. The traditional definition of status has been 30 min, however, the duration parameter is highly controversial and has created a flux in our definition of SE. The operational definition of SE proposed by Lowenstein et al.[21] is a continuous, generalized, convulsive seizure lasting greater than 5 min, or two or more seizures during which the patient does not return to baseline consciousness. In our study patients of SE were defined as continuous or repeated seizure activity for more than 5 min without recovery of consciousness.[22] Pregnant women, children less than 2 years of age and patients of hepatic encephalopathy were excluded from the study. Patients with myoclonic status epilepticus, neurological emergency requiring immediate surgical intervention, or contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs were also excluded. Only the first episode was included in the analysis if the patient was enrolled more than once by mistake. The intention to treat analysis was done and patients who left the treatment against medical advice were also included in the study.

Out of 3000 patients of epilepsy seen in outdoor and emergency ward, hundred patients were diagnosed as benzodiazepine resistant SE and included for the study after taking informed consent from conscious patients $\geq$18 years or from the parents in case of unconscious patients and patients under 18 years of age. These patients were randomly divided into groups A and B after matching for age and sex. Fifty patients in Group A received IV valproic acid in doses of 20 mg/kg (Limdi et al.[20]) as loading dose at rate of 40 mg/min[23–25] and 50 patients in Group B received IV phenytoin in the doses of 20 mg/kg (max. rate of 50 mg/min) after dilution with normal saline. All these patients were earlier given IV diazepam in doses of 0.2 mg/kg at 2 mg/min up to a maximum of 20 mg before labeling as refractory to diazepam.[22] We used commercially available intravenous valproate (Encorate®, Sun Pharmaceuticals Ind. Ltd., India).

Status epilepticus was considered to end at the time when convulsive seizure ceased and the patient subsequently regained consciousness. Status epilepticus was considered ongoing when seizures were clinically evident or when clinically seizures ended but the patient remained comatose and an electroencephalogram (EEG) indicated ongoing electrical seizure activity, or when the patient remained unconscious and subsequently had a convulsive seizure requiring treatment with an antiepileptic drug. We changed the therapy if life-threatening seizures were continued as per the standard protocol used in management of status epilepticus. All patients were monitored for the vitals viz. pulse, blood pressure, respiration, electrocardiogram (ECG), seizure activity, Glasgow coma scale (GCS), wherever required every 5 min for 2 h, then every 15 min for 12 h. All patients were followed for 7 days for seizure outcome and adverse events. EEG was done in all patients and repeated whenever required. Patients were followed up for 7 days to measure the outcome. All cases were investigated for complete blood count, blood sugar, serum electrolytes, blood urea, serum creatinine

Table 1 Etiology of status epilepticus

S. no.	Etiology	Group A (n = 50)	Group B (n = 50)	Total no. of cases (n = 100)
1	Antiepileptic drug withdrawal/noncompliance	12	14	26
2	Inflammatory granuloma (NCC[a]/tuberculoma)	12	12	24
3	CNS infections	10	12	22
4	Primary generalized seizure	8	6	14
5	Cerebrovascular accidents	2	2	4
6	Exrtradural hematoma	2	0	2
7	JME	2	0	2
8	Brain metastasis	2	0	2
9	Chronic renal failure	0	2	2
10	Eclampsia	0	2	2

[a] NCC — neurocysticercosis.

and liver enzymes. Cerebrospinal fluid examination and computed tomography/magnetic resonance imaging scans of brain to determine the etiology of seizure were also performed.

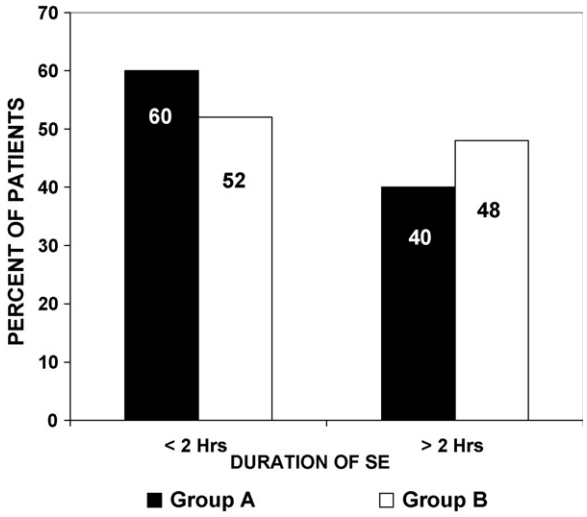
Treatment was considered successful when all motor or EEG seizure activity ceased within 20 min after the beginning of the drug infusion and there was no return of seizure activity during the next 12 h. Patients were switched over to the other group if seizures were not controlled or recurrence present with in 12 h of the treatment. Secondary study end points were in-hospital complications and neurological outcome at discharge. The safety and efficacy of the two drugs in each group were studied and the response was compared between the two groups in terms of significance using Student's t test.

Results

In the present study mean age of patients in Group A was 27.4 ± 16.8 years and Group B was 27 ± 15.1 years. There were 35 (70%) males in Group A, 32 (64%) in Group B and 15 (30%) females in Group A and 18 (36%) in Group B. There were 22 patients below 18 years of age in Group A, and 16 patients in Group B. The most common etiology of SE was antiepileptic drug noncompliance or withdrawal in 12 (24%) patients in Group A and 14 (28%) in Group B, while the other etiologies included inflammatory granuloma [12 (24%) in Group A and 12 (24%) in Group B], CNS infections [10 (20%) in Group A and 12 (24%) in Group B], primary generalized epilepsy [8 (16%) in Group A and 6 (12%) in Group B], stroke [2 (4%) in Group A and 2 (4%) in Group B] and head injury with exrtradural hematoma 2 (4%); in majority of patients (Table 1). The illnesses associated with SE (Table 2) were septicemia in 14 (14%) patients, viral fever in 8 (8%) and pulmonary tuberculosis in 6 (6%). Other comorbid conditions included chronic suppurative otitis media (CSOM), diabetes mellitus and renal failure. In 60 cases there was no significant associated illness. The duration of SE at the time of presentation (Graph 1) was <2 h in 60% (30/50) in Group A and 52% (26/50) in Group B. Interestingly, 40% (20/50) of Group A and 48% (24/50) of Group B were admitted >3 h after onset of SE. In these cases seizure activity had seized to occur 30 min after the seizure onset, but

Table 2 Associated illnesses in patients of SE

S. no.	Associated illnesses	No. of cases
1	Septicemia	14
2	Pulmonary tuberculosis	6
3	Viral fever	8
4	CSOM	4
5	Diabetes mellitus	2
6	Cortical venous thrombosis	2
7	CA lung	2
8	Renal failure	2
9	None	60



Graph 1 Duration of status epilepticus.

Table 3 Response to treatment in patients of status epilepticus

Response	Group A ($n = 50$)		Group B ($n = 50$)	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
SE controlled	44 ($n = 50$)	88 [*]	42 ($n = 50$)	84 [*]
Not controlled	6 ($n = 50$)	12	8 ($n = 50$)	16
SE <2 h	30 ($n = 30$)	100 [**]	25 ($n = 26$)	96 [†]
SE >2 h	14 ($n = 20$)	70 [**]	17 ($n = 24$)	71 [†]
Treated with both drugs	4 ($n = 7$) [‡]	57	2 ($n = 5$) [‡]	40

[*] $p > 0.05$.
[**] $p < 0.05$.
[†] $p < 0.05$.
[‡] $p > 0.05$.

they failed to regain consciousness by the time of hospital admission. In Group A, six cases were not controlled on IV VA, of these one patient left against medical advice and five cases were treated with IV phenytoin out of which two were controlled. Eight cases of Group B were not controlled with IV phenytoin, out of which seven cases were treated with IV VA, four cases were subsequently controlled and three were refractory to both the study drugs (Table 3). One patient left against medical advice (Table 4). Thus, twelve patients of SE were common in both groups and out of them six patients (50%) were refractory to both the drugs.

IV VA was successful in 88% and IV phenytoin in 84% ($p > 0.05$) patients of SE (Table 3). There was significant difference in response to treatment in patients of SE <2 h and SE >2 h in Group A (100% versus 70%) ($p < 0.05$) and Group B (96.15% versus 70.83%) ($p < 0.05$), respectively (Table 3). Among patients <18 years of age, 20 of the 22 Group A patients and 12 out of 16 Group B patients responded to treatment, 2 Group B patients responded to IV VA while the others did not respond to either drugs. There were no significant differences among the treatments with respect to recurrence during the 12 h study period or the outcome at 7 days. Mortality rate in both the groups was 8% (4/50 in Group A and 4/50 in Group B) (Table 4). One (2%) patient in Group A and one (2%) patient in Group B left the treatment against medical advice due to the cost of total treatment (Table 4). Mild elevation of liver enzymes was found in 8% (4/50) cases treated with IV VA while 12% (6/50) patients of Group B developed hypotension and 4% (2/50) developed respiratory depression (Table 5).

Discussion

Both the groups A and B were age and sex matched. The majority of the patients were of young age in both groups. In our study IV VA in doses of 20 mg/kg (Limdi et al.[20]) as loading dose at rate of 40 mg/min. The US Food and Drug Administration approved the IV formulation of valproic acid in 1996, with the original rate of 20 mg/min.[23] Although earlier studies established the safety of IV administration of valproate, slow infusion rates limited its use in emergency situations.[24,26] In the past 5 years, several studies have demonstrated the safety of rapid administration (up to 6 mg/kg/min)[23–25] of IV VA loading doses (up to 45 mg/kg)[26] and efficacy (ranging from 66% to 100%) in acute repetitive seizures and SE.[24]

According to studies from Western countries, the major etiologies of SE in adults include antiepileptic noncompliance, ethanol/drug related, metabolic disorders and anoxia/hypoxia.[27–29] However, antiepileptic drug withdrawal/noncompliance (26/100, 26%), inflammatory granuloma (24/100, 24%), CNS infections (22/100, 22%) dominate as the etiological causes in the current study, underscoring the importance of infections as one of the major, yet treatable, cause of SE in this tropical country.

Table 4 Outcome and follow up of the patients

Outcome	Group A ($n = 50$)	Group B ($n = 50$)
Recurrence in 12 h	6 [*]	8 [*]
Recurrence in 24 h	0	0
Mortality	4	4
Left against medical advice	1	1

[*] p value > 0.05.

Table 5 Adverse effects of therapy

Adverse effects	Group A ($n = 50$)	Group B ($n = 50$)
Hypotension	0	6
Respiratory depression	0	2
Mild elevation of SGPT	4	0
Total adverse events	4 [*]	8 [*]

[*] p value > 0.05.

Neurocysticercosis and CNS infections are considered as major etiological factors for epilepsy in many Indian studies reported earlier.[30]

In the present study, status epilepticus was interrupted successfully in 88% in Group A and 84% in Group B ($p > 0.05$). It was comparable to the result of other studies. Czapinski and Terezynski[18] in 1998 reported an 80% success rate in interrupting SE in a series of 20 adult patients using IV valproic acid in a bolus dose of 15 mg/kg followed by an infusion of 1 mg/kg/h. Peters and Pohlmann-Eden[19] have reported 85.6% success in controlling SE in a series of 102 adult patients using IV VA.

In our study 40% of Group A and 48% of Group B were having SE >2 h at the time of presentation, however, in these cases overt seizure activity had seized to occur 30 min after the seizure onset but they failed to regain consciousness at the time of hospital admission. The duration of SE was considerably prolonged as compared to other studies[12,28,31] reported from the developed countries. This delay in presentation might be attributed to the lack of awareness amongst the general public, inadequacy of medical and health services in this part of the world and the ignorance amongst the treating physicians regarding the need for emergency management of SE. The response to treatment was significantly better in patients having SE <2 h than SE >2 h in both the groups ($p < 0.05$). Limdi et al.[20] used IV valproic acid in a series of 63 patients of SE with an average dose of 31.5 mg/kg and found an overall efficacy of 63.3%. A better response was achieved in patients in whom SE had lasted <2 h before treatment. The delayed response in control of SE was associated with longer duration between onset of SE to beginning of therapy and underlying comorbid conditions in patients of SE as reported in other studies.[28,31]

In six patients of Group A (IV VA) and eight patients of Group B (IV phenytoin) recurrence of seizures was noted within 12 h after successfully ending the first episode of SE. There was no significant difference in response to SE after switching over to other drug in either of the group. Six out of twelve patients of SE were refractory to both the drugs suggesting some common mechanism of antiepileptic drug activity of both the drugs. No recurrence of seizures was noted within 1 week of follow-up in either of the groups suggesting no difference in neurological outcome at discharge in both groups.

In this study IV VA was well tolerated in patients of SE in comparison to IV phenytoin. Mild elevation of liver enzymes (SGPT) was noted in four cases treated with IV VA whereas side effects like hypotension (six cases), respiratory depression (two cases) were noted in patients who were loaded with IV phenytoin. No fall in BP or respiratory depression was noted in patients treated with IV VA, therefore it seems to be safe in patients having cardio-respiratory disease. There was no significant difference with respect to total adverse events in the two groups ($p > 0.05$). Limdi and Faught[32] described the safety of rapid infusion of valproic acid in doses ranging from 33.3 to 555 mg/min (median, 200 mg/min) without serious adverse effects. Venkataraman and Wheless[25] have also shown the safety of rapid loading doses of IV VA (mean dose 24.2 mg/kg and target infusion rates 3 or 6 mg/kg/min). Wheless et al.[33] in 2004 demonstrated that IV VA administered to patients with epilepsy at rates of infusion of up to 6 mg/kg/min and doses of up to 30 mg/kg does not cause clinically significant negative effects on blood pressure and pulse rate and caused only mild-to-moderate, reversible adverse events. The data given by Sinha and Nariotoku[34] also demonstrated that IV VA loading is well tolerated, even in patients with cardiovascular instability (review of hospital records of 13 patients with SE and hypotension).

In our study 22 patients were below 18 years of age in Group A, 20 cases were controlled with IV VA. In Group B, 16 patients were below 18 years of age out of which four cases were refractory reflecting no relation of the response of the drug to the age of the patient. Two responded to IV VA while the other patients were refractory to both drugs. Status epilepticus was controlled in 92% (92/100) of patients in total. Overall mortality was noted in 8% (8/100) of patients and two patients left against medical advice in total. These data suggest improvement from previous studies[15,28,31] reflecting improved care of the patients, change in operating definition of SE (from >60 min to >10 min and operating definition of >5 min) and high success with newer drugs like IV VA. Outcome of SE is determined by age, duration of status, cause of SE and other comorbid conditions as reported in other studies.[32,25] Acute processes that cause SE such as electrolyte abnormalities, renal failure, sepsis, stroke, head trauma and hypoxia are associated with high mortality, especially those occurring after hypoxia and in older patients.

Conclusions

In our present study IV VA was found to be as effective as IV phenytoin, with better tolerability as compared to IV phenytoin. IV VA can be used to treat all types of status including myoclonic status, where, this is the only drug which is effective. IV VA can be used as first line of treatment of SE after

benzodiazepines as an alternative to phenytoin, especially in patients of cardio-respiratory disease. The response to treatment was better in patients of SE <2 h than >2 h reflecting need of immediate treatment. The prolonged duration of SE at admission suggests requirement for increased awareness of immediate treatment of this fatal neurological disease among health workers and physicians in this part of developing world.

References

1. Shorvon S. *Status epilepticus: its clinical features and treatment in children and adults*. Cambridge: Cambridge University Press; 1994.
2. Hauser WA. Status epilepticus: epidemiologic considerations. *Neurology* 1990;**40**:9—13.
3. Aicardi J, Chevrie JJ. Convulsive status epilepticus in infants and children. A study of 239 cases. *Epilepsia* 1970;**11**:187—97.
4. Salas-Puig J, Suarez Moro R, Mateos V. Status epilepticus. *Neurologia* 1996;**11**(Suppl. 34):108—21.
5. Goldberg MA, McIntyre HB. Barbiturates in the treatment of status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status epilepticus: mechanisms of brain damage and treatment, vol. 34. Advances in neurology*. New York: Raven Press; 1983. p. 499—503.
6. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;**38**:202—7.
7. Crawford TO, Mitchell WG, Fishman LS, Snodgrass SR. Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology* 1988;**38**:1035—40.
8. Wilder BJ. Efficacy of phenytoin in treatment of status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status epilepticus: mechanisms of brain damage and treatment, vol. 34. Advances in neurology*. New York: Raven Press; 1983. p. 441—6.
9. Leppik IE, Patrick BK, Cranford RE. Treatment of acute seizures and status epilepticus with intravenous phenytoin. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status epilepticus: mechanisms of brain damage and treatment, vol. 34. Advances in neurology*. New York: Raven Press; 1983. p. 447—51.
10. Von Albert H-H. A new phenytoin infusion concentrate for status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status epilepticus: mechanisms of brain damage and treatment, vol. 34. Advances in neurology*. New York: Raven Press; 1983. p. 453—6.
11. Sutherland JM, Tait H. *The epilepsies: modern diagnosis and treatment*. Edinburgh, Scotland: Livingstone; 1969.
12. Delgado-Escueta AV, Enrile-Bacsal F. Combination therapy for status epilepticus: intravenous diazepam and phenytoin. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. *Status epilepticus: mechanisms of brain damage and treatment, vol. 34. Advances in neurology*. New York: Raven Press; 1983. p. 477—85.
13. Crawford TO, Mitchell WG, Snodgrass SR. Lorazepam in childhood status epilepticus and serial seizures: effectiveness and tachyphylaxis. *Neurology* 1987;**37**:190—5.
14. Gabor AJ. Lorazepam versus phenobarbital: candidates for drug of choice for treatment of status epilepticus. *J Epilepsy* 1990;**3**:3—6.
15. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:854—9.
16. Walker M. Status epilepticus: an evidence based guide. *BMJ* 2005;**331**:673—7.
17. Rosenow F, Arzimanoglou A, Baulac M. Recent developments in treatment of status epilepticus: a review. *Epileptic Disord* 2002 Oct;**4**(Suppl. 2):S41—51.
18. Czapinski P, Terezynski A. Intravenous valproic acid administration in status epilepticus. *Neurol Neurochirug Polaska* 1998;**32**:11—22. [Article in polish. Only Medline abstract reviewed].
19. Peters CN, Pohlmann-Eden B. Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005;**14**(3):164—9.
20. Limdi NA, Shimpi AV, Faught E, Gomez CR, Burneo JG. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 2005;**64**(2):353—5.
21. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia* 1999;**40**:120—2.
22. Walker MC, Shorvon SD. Emergency treatment of seizures and status epilepticus. In: Shorvon SD, Perucca E, Fish D, Dodson WE, editors. *The treatment of epilepsy*. Oxford: Blackwell Publishing Ltd.; 2004. p. 233.
23. Ramsay RE, Cantrell D, Collins SD, Walch JK, Naritoku DK, Cloyd JC, et al. Safety and tolerance of rapidly infused Depacon. A randomized trial in subjects with epilepsy. *Epilepsy Res* 2003;**52**:189—201.
24. Hodges BM, Mazur JE. Intravenous valproate in status epilepticus. *Ann Pharmacother* 2001;**35**:1465—70.
25. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. *Epilepsy Res* 1999;**35**(2):147—53.
26. Wheeles JW, Venkatraman V. Safety of high intravenous valproate loading in epilepsy patients. *J Epilepsy* 1998;**11**: 319—24.
27. Lowenstein D, Alldredge B. Status epilepticus in an urban hospital in the 1980s. *Neurology* 1993;**43**:483—8.
28. DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults and the elderly. *Epilepsia* 1992;**33**(4): S15—25.
29. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective study population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;**46**(4):1029—35.
30. Murthy JMK, Yangala R. Etiological spectrum of symptomatic localization-related epilepsies: a study from South India. *J Neurol Sci* 1998;**158**:65—70.
31. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia* 1994;**35**(1):27—34.
32. Limdi NA, Faught E. The safety of rapid valproic acid infusion. *Epilepsia* 2000;**41**(10):1342—5.
33. Wheless JW, Vazquez BR, Kanner AM, Ramsay RE, Morton L, Pellock JM. Rapid infusion with valproate sodium is well tolerated in patients with epilepsy. *Neurology* 2004;**63**(8): 1507—8.
34. Sinha S, Nariotoku DK. Intravenous valproate is well tolerated in unstable patients with status epileticus. *Neurology* 2000;**55**(5):722—4.